REMARKS

Claims 1, 3-6, and 8-25 are pending in the present application. Citations to paragraph numbers throughout this response correspond to the published application (US 2004/0157292) unless otherwise indicated. Each rejection is addressed individually below.

I. 35 U.S.C. § 112, First Paragraph – Scope of Enablement

Claims 1, 3-6 and 8-25 were rejected for alleged lack of enablement "because the specification, while being enabling for the full-length nucleic acid of SEQ ID NO: 1, does not reasonably provide enablement for *variants* or *fragments* of SEQ ID NO: 1" (Office Action at page 4, second paragraph) (emphasis in original). Applicants respectfully disagree with this rejection.

Claims 1, 3-6, 8, 10, and 11 are directed to CatSper1 nucleic acids, including subsequences of an entire CatSper1 nucleic acid, sequences encoding subsequences of an entire CatSper1 protein, sequences sharing at least 80% identity with a CatSper1 sequence, and sequences capable of hybridizing to a CatSper1 sequence under specified stringency conditions. Claims 9 and 12-25 are all dependent claims.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). However, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 8th Ed., Rev. 6 (Sept. 2007) § 2164.01 at 2100-194 (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463 (Fed. Cir. 1984)).

Applicants submit that those of skill in the art would have no difficulty in making or using variants or fragments of SEQ ID NO: 1, the sequence for human CatSper1. Fragments of at least 10-18 consecutive bases can be used as probes or primers to detect the presence of CatSper1 (¶ 63), to generate antibodies against specific epitopes (¶ 64), to create transformed cell lines (¶ 81), or to generate transgenic animals (¶¶ 87-88). How to make or use probes,

primers, antibodies, transformed cell lines, and transgenic animals from the claimed fragments is well-known to those skilled in the art, and "[a] patent need not teach, and preferably omits, what is well known in the art." Nonetheless, the present application actually does teach how to use CatSper1 fragments to make and/or use transformed cell lines (¶¶ 80-82), transgenic animals (¶¶ 86-95, 210), and antibodies (¶¶ 105-111, 207).

The Nikpoor reference cited on page 3 of the Office Action further illustrates that Applicants' claims are enabled. Nikpoor teaches that "[r]ecently, the search for the calcium channels residing in sperm led to the cloning and characterization of a novel gene, named CatSper, which codes for a unique cation channel (Ren et al., 2001)." Applicants respectfully note that they are both authors of Ren *et al.*, *Nature* 413(6856):603-609 (2001) cited in Nikpoor, and that the instant application is based in part on that publication (*compare* Exhibit C of Applicants' Amendment of November 5, 2008 *with* Examples 1-7 at ¶¶ 202-225). As explained in Applicants' Amendment of November 5, 2008, Nikpoor used human testicular biopsies to compare:

> CatSper gene expression in subfertile patients with deficient sperm motility to that of subfertile or fertile patients with motile sperm .... Gene expression levels were examined by semi-quantitative RT-PCR ... , statistical analysis comparing the means between the two groups (Student's *t*-test) revealed a significant difference in the level of hCatSper gene expression ($P = 0.009$) (Nikpoor at page 126, col. 1, last paragraph through page 127, col. 1., first paragraph).

Nikpoor used short sequences from the CatSper sequence disclosed in the Ren publication to perform PCR:

> PCR primers for human samples were designed using previously described human CatSper (hCatSper) and beta-2microglobulin (hβ2m) sequences (GenBank accession numbers: AF407333 and NM-004048 respectively). Primers were designed using Genrunner software (version 3.02; Hastings Software Inc.) and were as follows: hCatSper forward, 5-TCTTCTGCATCTACGTGGTG-3'; hCatSper reverse, 5'-CTCTTCTCCAGCCTCAAATG-3'; hβ2m forward, 5'-TCGCGCTACTCTCTCTTTCTG-3'; hβ2m reverse, 5'-GCTTACATGTCTCGATCCCAC-3' (Nikpoor at page 125, col. 2, second paragraph).

Thus, fragments of SEQ ID NO: 1 as disclosed and claimed in the instant application were used by those skilled in the art as PCR primers. Accordingly, Applicants respectfully submit that the Nikpoor reference cited in the Office Action proves that one of ordinary skill in the art was enabled to make and use the invention of claims 1, 3-6, and 8-25 by the very same disclosure (Ren et al. 2001) which formed the basis for the present application.

The Office Action also states:

> As to the probability of a fragment of 10-18 bases of SEQ ID NO: 1 occurring randomly, the examiner agrees that this would be a very unlikely event. However, the probability of random occurrence does not speak to the enablement of short nucleic acids of SEQ ID NO: 1 or of nucleic acids having 80% homology to SEQ ID NO: 1 (Office Action at page 5, first paragraph).

Applicants respectfully submit that this assertion is irrelevant to the discussion of whether the instant claims are enabled. A sequence serves as a successful primer or probe when that sequence is specific to its target gene. The length of the primer or probe determines its specificity; the longer the sequence, the more likely it will be specific for its target gene. A single-nucleotide sequence, for example, will hybridize to every gene in the human genome and is therefore not selective for any single target gene. A longer sequence, however, occurs less frequently and is therefore more specific. For instance, a sequence of 10 consecutive bases is one of 4^{10} possibilities, or one in 1,048,576. A fragment of 18 consecutive bases is one of 4^{18} possibilities, or one in 68,719,476,736. Therefore, a specific fragment of 10-18 consecutive bases has a less than a one in a million chance of occurring randomly. Accordingly, a probe or primer directed to a specific fragment of 10-18 consecutive bases is highly likely to identify the target gene. In the instant case, a probe or primer directed to a specific fragment of 10-18 consecutive bases of SEQ ID NO: 1 is highly likely to detect the presence of CatSper1, and is therefore desirably selective. One of skill in the art can understand and appreciate the usefulness of such a primer or probe.

Accordingly, Applicants respectfully request that the rejection of claims 1, 3-8, and 8-25 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

II. 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1, 3-6, 8, 10, and 11 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not describe the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention. Applicants respectfully disagree.

Claims 1, 3-6, 8, 10 and 11 are described above.

The Office Action asserts that:

> Applicants have neither made nor used any variants of SEQ ID NO: 1 or its encoded polypeptide. Therefore applicants were not in possession of all or a significant number of variants of SEQ ID NO: 1 such that a genus is established (Office Action at page 6).

As an initial matter, Applicants submit that they were clearly in possession of the complete CatSper1 nucleic acid and protein sequences. As such, Applicants submit that those of skill in the art would recognize that they were clearly in possession of subsequences as recited in claim 1.

Furthermore, the specification teaches that "subsets of the CatSper1 nucleic acid sequences are provided for use as primers for nucleic acid amplification reactions, as probes in hybridization assays to detect CatSper1 sequences in samples of other nucleic acids, or as probes to distinguish normal or wild-type sequence from abnormal or mutant sequences" (¶ 63). Although Applicants may not have actually reduced to practice all such primers and probes, the filing of the instant application serves as a constructive reduction to practice (MPEP § 2138.05 at 2100-109, col. 1, second paragraph). "[T]he inventor need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application" (*id.*).

Figure 1A clearly shows an entire CatSper1 sequence and delineates the positions of the transmembrane, loop and pore regions. The specification also provides a list of sequences having high predicted antigenicity. Therefore, Applicants submit that those of skill in the art would clearly recognize that Applicants were in possession of the nucleic acids as recited in claims 3 and 4.

Given the complete CatSper1 nucleic acid sequence, one of skill in the art can clearly identify sequences with 80% identity to that sequence, or any subsequence thereof. Therefore, Applicants submit that those of skill in the art would clearly recognize that Applicants were in possession of the nucleic acids as recited in claim 5.

Given the complete CatSper1 nucleic acid sequence, and the experiments disclosed in the specification for detecting CatSper1 activity, one of skill in the art can clearly identify sequences with 80% identity to that sequence and retain the activity. Therefore, Applicants submit that those of skill in the art would clearly recognize that Applicants were in possession of the nucleic acids as recited in claim 6.

DNA hybridization experiments were well within the ability of those of skill in the art, at the time of filing. Given the complete CatSper1 nucleic acid sequence, and such routine skill, one of skill in the art can clearly identify sequences that hybridize under specified conditions. Therefore, Applicants submit that those of skill in the art would clearly recognize that Applicants were in possession of the nucleic acids as recited in claim 8.

Finally, with respect to claims 10 and 11, which substantially include the limitations of claims 6 and 8 discussed above, one of skill in the art, particularly in view of the teachings of the specification, can clearly produce the claimed operably joined sequences. Therefore, Applicants submit that those of skill would clearly recognize that Applicants were in possession of the nucleic acids as recited in claims 10 and 11.

For the foregoing reasons, Applicants respectfully request that the rejections of claims 1, 3-6, 8, 10, and 11 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

III. 35 U.S.C. § 102(b)

A. Sanger Centre

Claims 10 and 12 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated in view of Sanger Centre (1998, *Science*, 282:2012-2018, Accession No. Z82256.1) ("the Sanger Centre sequence"). The Office Action states:

> The Sanger Centre Consortium discloses a polynucleotide sequence encoding a nematode sodium channel which is 29% identical to SEQ ID NO: 1 in the instant application. There are several short identical areas where the nucleotides are the same, such as in the region of residues 174-181. This reference meets the limitations of claims 10 and 12 which recite "at least *a portion* of SEQ ID NO: 1," as well as hybridization steps that are not stringent (i.e., washing at 65°C).

(Office Action at page 8, first paragraph) (emphasis in original).

Claim 10 recites "a nucleotide sequence encoding a polypeptide having CatSper1 activity" and that hybridizes to a portion of SEQ ID NO: 1 under specific conditions, and "a heterologous regulatory region operably joined to said sequence such that said sequence is expressed." Claim 12 recites a kit for detecting at least a portion of a CatSper1 nucleic acid comprising an isolated nucleic acid of any one of claims 1, 3-6, and 8-11.

Under 35 U.S.C. § 102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

The Office Action provides no evidence that the Sanger Centre sequence has CatSper1 activity as recited in claim 10, or that the Sanger Centre sequence is operably joined to a heterologous regulatory region such that the sequence is expressed. The Sanger Centre sequence thus does not disclose "each and every element" of claim 10 as required by § 102(b).

Claim 12 recites a kit including a CatSper1 nucleic acid and means for detecting said nucleic acid. The Sanger Centre sequence discloses neither a kit nor means for detecting a nucleic acid. Therefore, the Sanger Centre sequence does not possess "each and every element" of claim 12 as required by § 102(b).

Therefore, Applicants respectfully request that the rejection of claims 10 and 12 under 35 U.S.C. § 102 be reconsidered and withdrawn.

B. Hillier

Claims 1, 3, 8, and 12 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated in view of Hillier, *et al.* (1997, Accession No. AA416682.1) ("Hillier").

Claims 1, 3, 8, and 12 are described above.

The Office Action asserts that Hillier "discloses a polynucleotide sequence encoding a calcium channel which is 19.3% identical to SEQ ID NO: 1 in the instant application and 99% identical from residues 1592 to 2056 of SEQ ID NO: 1" (Office Action at page 7, first full paragraph). The Office Action also asserts that Hiller discloses "a sequence encoding a transmembrane loop (specifically the alpha helix as described in the reference)" (*id.*).

As an initial matter, claim 12 recites a kit including a CatSper1 nucleic acid and means for detecting said nucleic acid. Hillier discloses neither a kit nor means for detecting a nucleic acid. Therefore, Hillier does not possess "each and every element" of claim 12 as required by § 102(b).

Furthermore, "[a] reference that is not enabling is not anticipating." *Forest Labs. Inc. v. Ivax Pharm Inc.*, 84 U.S.P.Q.2d 1099, 1103 (citing *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003)). "The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which posed the question: is the experimentation needed to practice the invention undue or unreasonable?" MPEP § 2164.01 at 2100-193.

Hillier merely discloses a nucleic acid sequence that is a "skeletal muscle calcium channel," and does not teach how to use the sequence disclosed. Significantly, Hillier fails to provide any utility whatsoever for the disclosed sequence. Therefore, Hillier fails to teach that any fragment of the Hillier sequence is useful as a CatSper1 fragment as disclosed in the instant application, and Hillier cannot anticipate claims 1, 3, 8, and 12.

Applicants respectfully note that there is a tension between the instant § 102(b) rejection in light of Hillier and the § 112, first paragraph, enablement rejection addressed above. Hillier presents no utility for the Hillier sequence, while Applicants have presented numerous utilities for the subject matter of the present claims. In fact, Applicants overcame a § 101 utility objection in the previous Office Action. If Applicants' claims are not enabled, as asserted by the Office Action, despite the numerous uses disclosed in the application, then the Hillier reference

certainly is not enabled. Accordingly, the Hillier reference cannot anticipate claims 1, 3, 8, and 12.

Therefore, Applicants respectfully request that the rejection of claims 1, 3, 8, and 12 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

CONCLUSION

In view of the amendment and arguments made herein, Applicants respectfully request reconsideration of all claims, and submit that the claims are in condition for allowance.

Applicants note that an initialed copy of the Form PTO-1449 submitted with the Information Disclosure Statement on February 11, 2004 was not returned by the Examiner. Applicants enclose a copy of that document and request that the Examiner return an initialed copy with the next Office Action.

Applicants believe that no fees are due with this Response. However, if such a fee is due, please charge it to Deposit Account No. 08-0219, referencing Attorney Docket No. 0110313.135US3.

Respectfully submitted,

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